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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/811,192	COMMUNI ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *1-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/077,173.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Invention III in the reply filed on March 23, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on March 23, 2006.

Claims 17-18 are under consideration.

Information Disclosure Statement

The information disclosure statement filed September 7, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. It is noted that the references that were considered were found in parent application, 09/077,173. However, neither the parent application nor the instant application contained the references that have been crossed off the IDS. In order for these references to be considered, Applicant must provide these references.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. Pages 18-20 of the specification contain a listing of references. If these references are to be considered, they must be indicated on an IDS and copies must be provided.

Specification

37 CFR 1.821(d) states: "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description of claims, even if the sequence is also embedded in the text or the description or claims of the patent application.

The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). Page 14 of the specification contains 2 sequences and Figure 1 comprises a sequence. SEQ ID NOs must be assigned to each of these sequences and the sequences must be provided on computer readable

format (CRF) and on paper. A statement indicating that the sequences on the CRF and paper format are the same must also be provided.

Appropriate correction is required.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 17 and 18 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial utility or a well established utility. According to the Revised Utility Examination Guidelines, see the Federal Register, Vol. 66, No. 4, pp. 19092-1099 (January 5, 2001), also available at http://uspto.gov/web.menu.utility.pdf, the following definitions of credible, specific, and substantial apply.

A credible utility is one that a person of ordinary skill in the art would accept as currently available. An assertion is considered credible unless (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the Applicant to support the assertion of utility. A credible utility is assessed from the

standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use.

A specific utility is one that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention.

A substantial utility is one that defines a real world use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context of use are not substantial utilities. Research that involves studying the properties of the claimed product itself does not constitute a substantial utility.

See also MPEP 2107-2107.02, and *Brenner, Comr. Pats. v. Manson*, 148 USPQ 689 (US SupCt 1966).

The instant claims are drawn to a transgenic non-human mammal comprising a disruption in its endogenous P2Y4 receptor gene. However, the specification provides no guidance for the use of the claimed non-human mammals. Further, the art teaches that the claimed non-human mammals have no known utility. Robaye, et al., 2003, Molecular Pharmacology, 63: 777-783, indicates that, "no physiological role of the P2Y4 receptor has yet been established and its pharmacotherapeutic potential thus remains uncertain (Robaye et al., page 777, 1st col., 1st parag.)." Robaye et al. teach that P2Y4 knockout mice were generated and that, "these mutant mice are grossly normal, and the only phenotypic abnormality that we have detected so far is the disappearance of the jejunal chloride secretory response to UTP and ATP (Robaye et al., page 781, 2nd col., 1st parag. bottom to page 782, 1st col., 1st parag.)." However, whether this phenotype

can be extrapolated to humans remains yet to be determined (Royabe et al., page 781, 1st col., 2nd parag.). Thus, the prior art, while identifying P2Y4 as a G-protein coupled receptor, does not teach that mice lacking P2Y4 expression have any phenotype related to any disease or symptom of disease associated with P2Y4.

Thus, in view of the discussion above, no specific, substantial, or well-established utility has been ascribed to the claimed transgenic non-human mammals encompassed by the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed

invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

While the specification contemplates that the invention encompasses a transgenic non-human mammal comprising a homologous recombination knockout of the P2Y4 receptor (specification, page 5, 2nd parag.), nothing in the specification provides guidance as to how to predictably arrive at and use the claimed invention. While the specification teaches the tissue distribution of P2Y4 (specification, page 16) and that functional studies were carried out in cells transfected with a nucleic acid construct comprising a nucleic acid sequence encoding P2Y4 (specification, pages 16-18), nothing in the specification provides guidance as to how an artisan would arrive at a non-human model of disease comprising a disruption of P2Y4 in its genome. More specifically, nothing in the specification teaches that any transgenic non-human mammal encompassed by the claims was made. This is an issue because the art teaches that the art of transgenesis is unpredictable.

The claims broadly encompass any transgenic non-human animal comprising a targeted mutation of P2Y4. However, at the time of filing, the art teaches that the phenotypes of knockout mice were unpredictable. In addition, the art did not consider the correlation between any observed mouse phenotypes and human disease phenotypes as predictable. Doetschmann et al. teaches that "[o]ne often hears the comment that genetically engineered mice, especially knockout mice, are not useful because they frequently do not yield the expected phenotype, or they don't seem to have any phenotype (Doetschmann,1999, Lab. Animal Sci., 49: 137-143, see page 137, column 1, paragraph 1)." Doetschmann provides numerous examples of instances in which genes considered well-characterized *in vitro* have produced unexpected phenotypes or indiscernible or no phenotypes in transgenic or knockout mice. Moens et al. further teaches that different mutations in the same gene can lead to unexpected differences in the phenotype observed. Moens et al. shows that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embyronic stem cells, one leaky and one null (Moens et al.,1993, Development, 119: 485-499). Further, the art demonstrates the unpredictability of making a mouse model for human disease by disrupting the murine gene. Jacks et al. teaches that although retinoblastoma (Rb) gene mutations in humans are associated with retinal tumors, Rb gene knockout mice had tumors in the pituitary gland rather than the retinas (Jacks et al., 1992, Nature, 359: 295-300). Likewise, whereas HPRT deficiency in humans is associated with Lesch-Nyhan syndrome, a severe neurological disorder, HPRT-deficient mice are phenotypically normal (Kuehn et al.,1987, Nature,

326, 295-298 and Jaenisch, 1988, Science, 240, 1468-1474). Thus, the art at the time of filing clearly establishes the unpredictability of determining the phenotype of transgenic or knockout mouse even when the activity of the gene has been extensively studied *in vitro*, and further establishes the unpredictability of generating a mouse model for human disease based on the activity of the gene in humans.

In addition to these issues, Racay, 2002, Bratisl Lek Listy, 103: 121-126, teaches that:

> "mutations of some genes led to phenotype showing severe defects, which did not correspond to any clinically important disorder, indicating either high *in vivo* stability of the gene or the interspecies differences. From the view of human medicine, the differences among the species (it means the differences in genetic background, gene expression, metabolism, and signal transduction) represent the main limitation of the use of genetically modified animals as models of human diseases. Therefore some results acquired by this approach can not be applied in human medicine because of the differences between rodents and human beings (Racay, page 124, under point 5)."

As this issue applies to the instant invention, it is unclear whether any knockout non-human mammal comprising a disruption in P2Y4 is a model of human disease. Robaye et al. 2003, Molecular Pharmacology, 63: 777-783 teach that while a transgenic mouse comprising a homozygous disruption in P2Y4 was made, that the use of the mouse is contingent upon whether the results in mouse can be extrapolated to humans (Robaye et al., page 782, 1st col., 2nd parag.). As such, the use of the mouse as a model of disease or use in an application for human therapy is not clear at the time of filing.

In addition to the phenotypes of knockout mice being unpredictable, the art teaches that while the promise of gene targeting had been to reveal the *in vivo* function

of a gene of interest, the functional relevance of gene targeting has been questioned because the mutation might lead to an avalanche of compensatory processes (up- or downregulation of gene products) and resulting secondary phenotypical changes. Thus, a null mutant organism might not only lack the produce of a single gene, but might also possess a number of developmental, physiological, or even behavioral process that have been altered to compensate for the effect of the null mutation (Gerlai, 1996, Trends Neurosci, 19: 177-181, page 177, 1st col., 1st parag.). Gerlai teaches an example wherein background genotype can confound the exhibited phenotypes. Targeted disruption of a gene of interest, α, might lead to changes in expression of alleles b and B for gene β. A regulatory change in gene β might lead to different phenotypic changes, depending on which allele (b or B) is present in the organism with the null mutation in gene α. The upshot of this problem is that due to this polymorphism in the genetic background, one cannot conclude for certain that a phenotypic change exhibited in a null-mutant mouse resulted from the null mutation or to the genetic background (Gerlai, page 177, 1st col., under "Polymorphism in the genetic background might make the results of gene-targeting studies difficult to interpret"). As this issue applies to the instant invention, as it is unclear what biological relationship P2Y4 has with any phenotype, an artisan would need to undergo undue experimentation to determine the relationship between phenotype and gene and to also undergo further experimentation to characterized whether the phenotype in the mouse has any relationship to any human disease.

The art teaches that an artisan cannot extrapolate biological function across

members of a gene family. The art teaches that the G-protein coupled receptor (GPCR) family, of which P2Y4 is a member, is an immense superfamily of several hundred members which can be classified into families and subfamilies. Table 1 in Morris and Mablon, 1999, Physiological Reviews, 79: 1373-1430, lists known GPCRs at that time and this table indicates how diverse GPCRs are in function. As such, while GPCRs may commonly have a similar structure, an artisan cannot predict that one GPCR will have the same biological activity as another GPCR. Subsequently, an artisan cannot predict the biological role P2Y4 has in any mammal.

The claims broadly encompass any transgenic non-human mammal. However, at the time of filing, the art teaches that the only known non-human mammal in which embryonic stem (ES) cells can be obtained was for mouse. This is because mice are the only mammals in which ES cells can be generated and which chimerism from ES cells extend to the germline (Murray, et al. 1999, *Transgenic Animals in Agriculture*, CAB International: Oxon, pages 58-61, page 60 2nd parag.). Further, according to Murray, et al. (1999, *Transgenic Animals in Agriculture*, CAB International: Oxon, pages 58-61), the "isolation of ES cells has not been accomplished unequivocally in other species, including in domestic livestock (Murray, et al., page 59, lines 3-4)." As the teachings of Murray et al. apply to the instant invention, while the art teaches how to make transgenic mice with ES cells, neither the specification nor the art teaches how to obtain ES cells from other species of mammals such that an artisan can obtain a line of transgenic non-human mammals comprising the knockout construct. Thus, while the art teach transgenic mice, the specification and the art do not provide guidance for the full

breadth of the claims.

Thus, for these reasons, the specification and art do not provide guidance for an artisan to arrive at the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 recites the limitation "said mouse" in claim 17. There is insufficient antecedent basis for this limitation in the claim, as there is no "mouse" prior to the mouse in line 4. Alternatively, if the scope of claim 17 is "mouse," then claim 18 is redundant.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with

the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application No.10/753,695 and 09/077,173 (now U.S. Patent 6,790,626), fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Neither Application 10/753,695 nor 09/077,173 provides adequate support or enablement for a transgenic non-human mammal which has a phenotypic abnormality due to a disruption in a P2Y4 gene. See the rejections under 35 U.S.C. 112, first parag., above, for an in depth discussion regarding enablement. Subsequently, the priority date of the instant application is March 26, 2004.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 17 and 18 are rejected under 35 U.S.C. 102(a) as being anticipated by Robaye et al., 2003, Molecular Pharmacology, 63: 777-783.

Robaye et al. teach transgenic mouse comprising a DNA targeting construct in its genome, wherein upon integration of the transgene construct, the transgenic mice exhibit no expression of P2Y4 (Robaye et al., page 778, under "Generation of P2Y4-

Deficient Mice" and page 779, 1st col., 2nd parag. under "Generation of P2Y4-Null Mice" to 2nd col., 1st parag.).

Thus, Robaye et al. anticipate claims 17 and 18.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

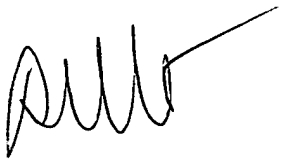
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image

problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JH



Application No.:
10/811,192

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _____

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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